EFFECTS OF PREOPERATIVE CHEMOTHERAPY AND RADIATION THERAPY ON HUMAN BRONCHIAL BLOOD FLOW

Ryoji Yamamoto, MD
Hirohito Tada, MD
Akihiro Kishi, MD
Takashi Tojo, MD

Objective: We investigated the relationship between bronchial mucosal blood flow around the area of lung resection and the state of healing of the bronchial stump in patients after chemotherapy with or without radiation therapy.

Methods: Ninety patients with primary lung cancer were divided into the following 3 groups: group A, 72 patients who had no preoperative therapy; group B, 10 patients who had chemotherapy; and group C, 8 patients who had chemoradiation (60 Gy) therapy. Bronchial mucosal blood flow was measured preoperatively, intraoperatively, and postoperatively (days 8-10) with a laser Doppler flowmeter.

Results: In groups A and B bronchial mucosal blood flow was preserved sufficiently around the surgical site, and the healing of the bronchial stump was satisfactory. On the contrary, preoperative blood flow in group C was 70% of the preoperative value in group A and decreased further intraoperatively. Healing of the bronchial stump was poor, and a bronchopleural fistula occurred in one patient of group C.

Conclusion: Preoperative chemoradiation therapy may adversely affect bronchial mucosal blood flow and healing of the bronchial stump, although lymphadenectomy and preoperative chemotherapy had little effect. It is recommended that the bronchial stump should be covered with pedicled viable tissue after chemoradiation therapy for prophylaxis against bronchial complications. (J Thorac Cardiovasc Surg 2000;119:939-45)

A number of reports[1-3] showed that preoperative chemotherapy with or without radiation therapy increased not only the difficulty in surgical technique but also the risk of bronchial complications after lung resection. The main cause of the complications is considered to be a reduction in bronchial mucosal blood flow as a result of these therapies.[4-6] However, to our knowledge, there have been no detailed studies published about the effects of these therapies on bronchial circulation and postoperative healing of the bronchial stump in human subjects. This report describes the relationship between bronchial mucosal blood flow (BMBF) and the state of healing of the bronchial stump in patients after chemotherapy with or without radiation therapy.

From the Division of Pulmonary Surgery, Osaka City Medical Hospital, Osaka, Japan.

Received for publication June 24, 1999; revisions requested Sept 17, 1999; revisions received Nov 8, 1999; accepted for publication Dec 13, 1999.

Address for reprints: Ryoji Yamamoto, MD, Division of Pulmonary Surgery, Osaka City Medical Hospital, 2-13-22, Miyakojima-hondori, Miyakojima-ku, Osaka 534-0004, Japan.

0022-5223/2000 $12.00 + 0 **12/1/105053**
doi:10.1067/mtc.2000.105053

Methods

Patients. Ninety patients with primary lung cancer were examined between April 1995 and March 1996. Informed consent was obtained from each patient before the procedure to measure BMBF. The patients were divided into the following 3 groups: group A, 72 patients with no preoperative therapy; group B, 10 patients given cisplatin-based induction chemotherapy who were operated on within 6 weeks after chemotherapy; and group C, 8 patients given cisplatin-based chemotherapy and concurrent 60 Gy of irradiation. All patients in group C had locally advanced inoperable disease and were given chemoradiotherapy in other hospitals. Because 5 of 8 were downstaged and the other 3 had local recurrence after complete remission, they were sent to our hospital for surgery. Therefore the intervals between irradiation and surgery were inconsistent: 2 months in 3 patients, 3 months in 1 patient, 9 months in 1 patient, 10 months in 1 patient, 3.5 years in 1 patient, and 5 years in 1 patient. Table I

Table I. *Preoperative characteristics of the 3 groups*

Variables	*Group A (n = 72)*	*Group B (n = 10)*	*Group C (n = 8)*	P *value*
Age (y)	63.0 ± 9.8	61.5 ± 9.4	62.5 ± 7.3	.9*
Sex				.3†
Male	43	8	7	
Female	29	2	1	
Performance status				.2†
0	28	1	1	
1	43	9	7	
2	1	0	0	
Pathologic type				.4†
Adenocarcinoma	41	3	3	
Squamous cell carcinoma	24	5	4	
Others	7	2	1	
Clinical stage				.06†
I	36	1	2	
II	9	3	3	
III	27	6	3	
Associated disease				.7†
Diabetes mellitus	9	0	1	
Cardiovascular disease	14	1	1	
Type of resection				.3†
Right pneumonectomy	1	—	1	
Upper lobectomy	21	4	2	
Middle lobectomy	8	—	—	
Lower lobectomy	12	—	—	
Left pneumonectomy	7	2	1	
Upper lobectomy	15	4	3	
Lower lobectomy	8	—	1	

**P* value determined by using 1-factor analysis of variance.
†*P* value determined by using the χ^2 test for independence.

shows preoperative characteristics of the 3 groups. In all patients mediastinal lymphadenectomy was performed, and bronchial arteries were cut. Patients with bronchoplasty were not included in this study. Only in group C, all bronchial stumps were covered with an intercostal muscle pedicle flap.

Measurement of BMBF. We determined BMBF by the technique of Sundset and colleagues[7] with a laser Doppler flowmeter (Periflux PF4001 Master and PF 306 Angled Endoscopic Probe; PERIMED, Stockholm, Sweden). In brief, preoperatively, BMBF was measured through a bronchial fiberscope (BF100T; Olympus, Tokyo, Japan). With breath holding, stable recordings for at least 10 seconds were recorded with a linear recorder (U-228; Nippon Denshi Kogaku, Kyoto, Japan). Results were expressed in arbitrary perfusion units (PU). BMBF was measured at the main carina, left second carina, right second carina, and third carina. Determinations were made 3 times at each site, and the mean of these 3 determinations was regarded as the value of BMBF. The measurements were not performed at the sites that had inflammation or tumor invasion. During surgery, the probe was directly attached to the mucosa of the concerned bronchial bifurcation from the bronchial stump after lymph node dissection and lobectomy was complete. Postoperative measurements were performed at the time of routine follow-up bronchoscopy on postoperative days 8 to 10. All measurements were done by the first author just after a bronchoscopist investigated the state of healing of the bronchial stump. Intraoperative and postoperative flux values were measured only at the bronchial bifurcation contiguous to the bronchial stump. When comparing the values of BMBF among 3 groups and within each group, we used the values at the bronchial bifurcation contiguous to the bronchial stump; preoperatively, the values at the site correspondent to this bifurcation were used. Preoperative value in group A at this site was set as the control value.

Seven patients in group A were examined just before surgery to evaluate the effects of general anesthesia and the lateral position on BMBF because the intraoperative flux value was measured under these conditions. All of these 7 patients had left lung cancer and were examined in the right lateral position. These 7 patients were intubated with a 9F intratracheal tube with an occlusion balloon through which the bronchial fiberscope could pass. Other patients in group A were intubated with a double-lumen tube through which the bronchial fiberscope could not pass.

In 7 individuals other than the patients in this study (3 with occult lung cancer and 4 with hemosputum), bronchoscopic examinations were performed twice within 3 to 24 weeks. BMBF was measured at these two times, making evaluation of reproducibility possible.

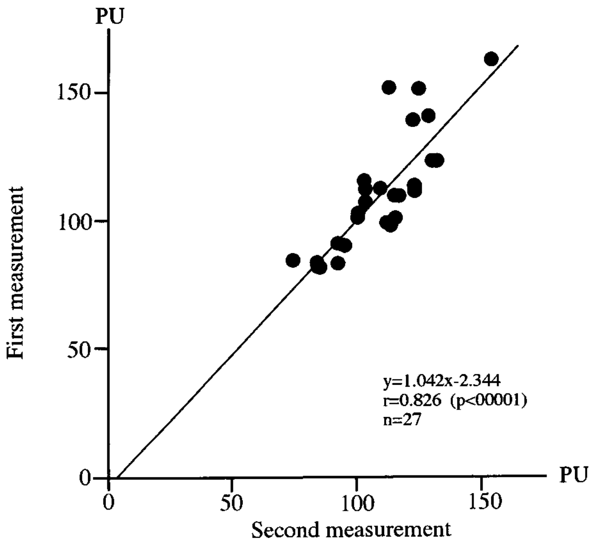

Fig 1. Reproducibility of measurements of bronchial mucosal blood flow. A good correlation was found between the two measurements at intervals of from 3 to 24 weeks.

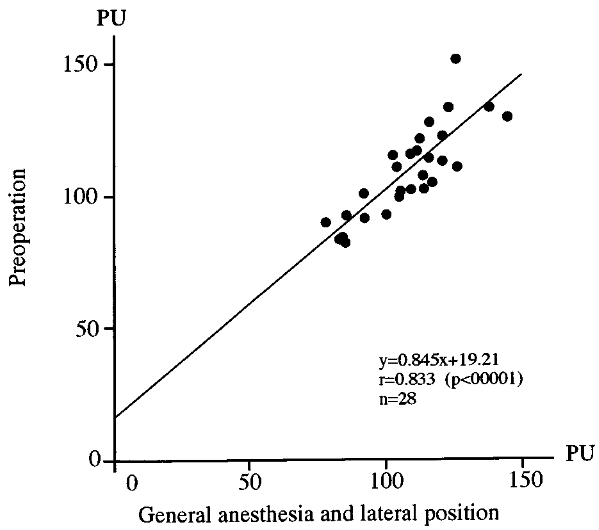

Fig 2. The effect of general anesthesia and the lateral position on BMBF. A good correlation was found between the two measurements.

Healing of the bronchial stump. Two bronchoscopists made the determinations of ischemic changes around the bronchial stump before the measurements of BMBF. Therefore the bronchoscopists were blinded to the obtained data about BMBF. Ischemic change was indicated by a white coating, ulceration, or necrosis of the bronchial wall around the stump.

Statistical analysis. All values are expressed as means ± SD when applicable. Clinical categorical variables were compared among 3 groups by using the χ^2 test or 1-factor analysis of variance after the Bartlett test. Simple regression was used to analyze the reproducibility and the effect of general anesthesia and the lateral position on BMBF. One-factor analysis of variance after the Bartlett test was used for comparison of variables of BMBF. When the analysis of variance revealed a significant interaction, the Fisher protected least significant difference post hoc test was done.

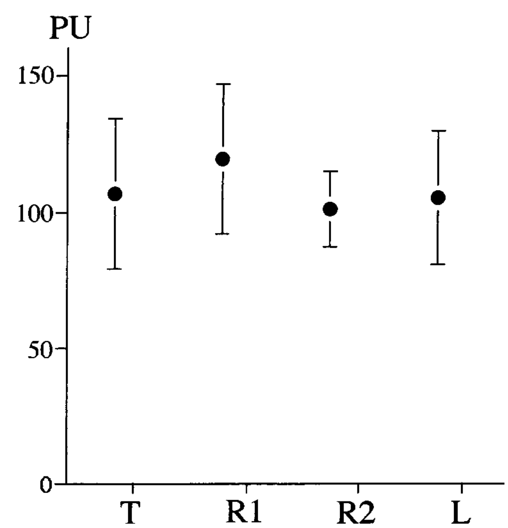

Fig 3. Preoperative bronchial mucosal blood flow in group A. No significant differences were demonstrated among the 4 locations (P = .79 by one-factor analysis of variance). *T,* First carina; *R1,* right second carina; *R2,* right third carina; *L,* left second carina.

Results

There were no significant differences among 3 groups with regard to age, sex, performance status, pathologic type and stage, associated disease, and type of resection (Table I). The time for measurement of BMBF was within 5 minutes preoperatively and within 1 minute intraoperatively and postoperatively.

Reproducibility of BMBF measurements. Reproducibility was evaluated by comparing the values of BMBF from two bronchoscopies at intervals of from 3 to 24 weeks in 7 individuals. There was a good correlation between the two investigations (r = 0.82, P < .0001; Fig 1).

The effects of general anesthesia and the lateral position on BMBF. There was also a good correlation between the preoperative values of BMBF and the values under general anesthesia and the lateral position (r = 0.83, P < .0001; Fig 2).

Preoperative values of BMBF in group A. The preoperative mean values of BMBF in group A ranged

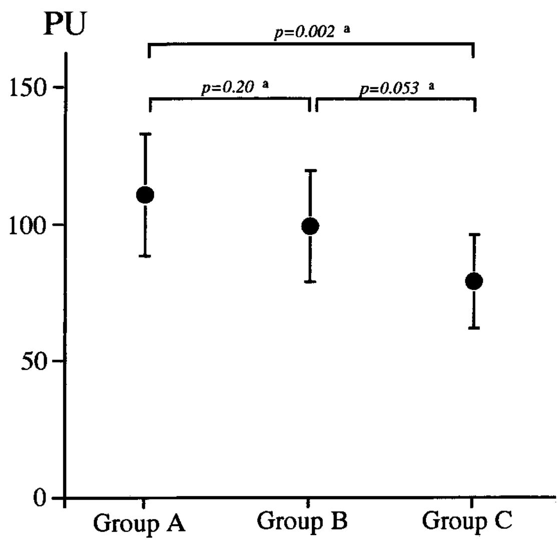

Fig 4. Preoperative bronchial mucosal blood flow of the 3 groups. Preoperative value in group C was significantly low in comparison with that of in group A (the control value). [a]*P* values are determined by using the Fisher protected least significant difference test.

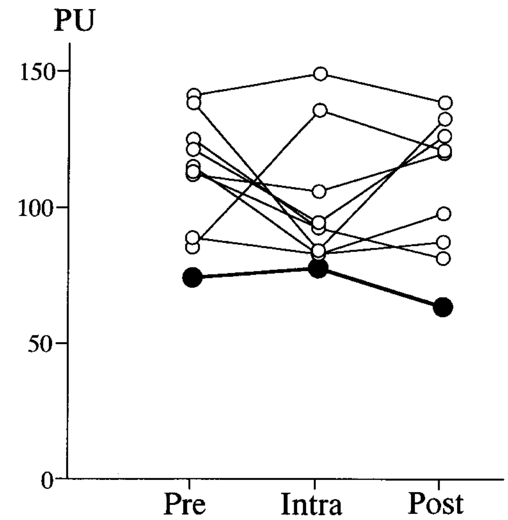

Fig 6. Changes of bronchial mucosal blood flow in group B. No significant differences were demonstrated among the preoperative, intraoperative, and postoperative time points (P = .53 by 1-factor analysis of variance). *Closed circles* and *thick line* indicate a patient with ischemic change at the bronchial stump. *Pre,* Preoperative; *Intra,* intraoperative; *Post,* postoperative.

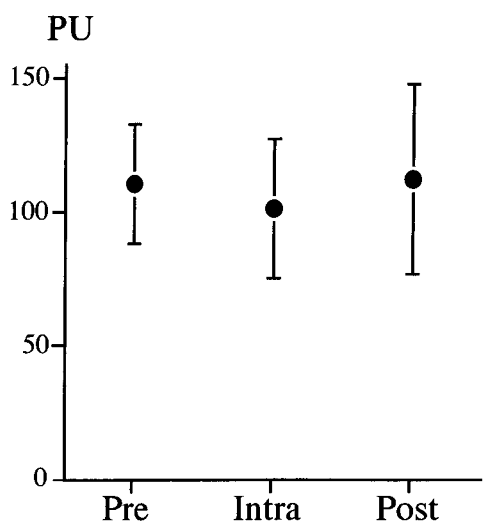

Fig 5. Changes of bronchial mucosal blood flow in group A. No significant differences were demonstrated at preoperative, intraoperative, and postoperative time points (P = .58 by 1-factor analysis of variance). *Pre,* Preoperative; *Intra,* intraoperative; *Post,* postoperative.

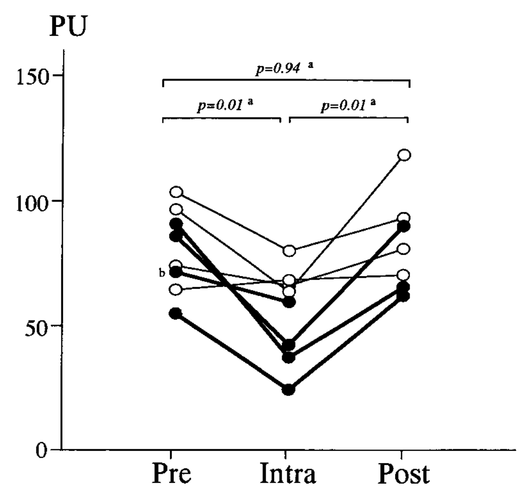

Fig 7. Changes of bronchial mucosal blood flow in group C. Intraoperative values were significantly low compared with preoperative and postoperative values. *Closed circles* and *thick lines* indicate patients with ischemic changes or bronchopleural fistula at the bronchial stump. [a]*P* values determined by using the Fisher protected least significant difference test; [b]patient with bronchopleural fistula. *Pre,* Preoperative; *Intra,* intraoperative; *Post,* postoperative.

from 108 to 112 PU among the 4 locations (Fig 3), with no significant differences among the locations (P = .8). The control value was 111.3 ± 22.3 PU.

Comparison of preoperative values of BMBF among 3 groups. Preoperative value of BMBF in group C (79.5 ± 17.1 PU) was 71.3% of that of the control value (P = .002; Fig 4). There were no significant differences between groups A and B (P = .20) or between groups B and C (P = .053). Preoperative value

Table II. *State of healing of bronchial stump*

	Group A (n = 72)	*Group B (n = 10)*	*Group C (n = 8)*	P *value*
State of healing				<.0001
No ischemic change	71	9	4	
Ischemic change	1	1	3	
Bronchopleural fistula	0	0	1	

P value was determined by using the χ^2 test for independence.

in group B was 99.7 ± 20.3 PU. In group C the BMBF at the site of the radiation field (n = 16) was 106.8 ± 24.5 PU, with no significant difference in comparison with the control value (*P* = .4; detailed data not shown).

Changes with time in BMBF. Changes in the value of BMBF in group A are shown in Fig 5. Although there were slight differences, no significant differences were demonstrated preoperatively, intraoperatively, and postoperatively (*P* = .6). Only one patient had ischemic changes at the bronchial stump. His preoperative, intraoperative, and postoperative flow values were 103.5, 91.2, and 88.4 PU, respectively.

Fig 6 shows the changes in group B, and again there were no significant differences within the times of the measurement (*P* = .5). One patient had moderately low flow values throughout the period (Fig 6, *thick line*), indicating ischemic change at the bronchial stump. His preoperative, intraoperatiave, and postoperative values were 74.3, 80.9, and 63.2 PU, respectively.

In group C (Fig 7) intraoperative BMBF decreased significantly in comparison with the preoperative (*P* = .01) and postoperative (*P* = .01) values. In the 4 patients with the lowest intraoperative values, ischemic changes at the bronchial stump were observed in 3, and a bronchopleural fistula developed in the residual one. There were no significant differences between preoperative and postoperative values (*P* = .9).

Bronchoscopic findings. Table II summarizes the state of healing of the bronchial stump. In group A healing was excellent, and slight redness and swelling were observed around the bronchial stump. Only 1 (1.4%) of 72 patients showed ischemic changes. Postoperative healing in group B was similar to that found in group A. Ischemic changes were observed in 1 (10%) of 10 patients. The values of BMBF in this patient were the lowest in group B (Fig 4, *thick line*). On the other hand, ischemic changes were seen in 3 patients, and a bronchopleural fistula developed in one patient (Fig 5, *thick line*) in group C. This patient with a bronchopleural fistula underwent right pneumonectomy 10 months after chemoradiation therapy. He had no associated diseases, but the tensile strength was strong when his bronchial stump was closed. Because he refused follow-up bronchoscopy, we could not obtain information on healing of his bronchial stump and postoperative BMBF. On postoperative day 22, a bronchopleural fistula occurred. Diagnosis was made on the basis of symptoms and chest roentgenography. The patient needed mechanical ventilation. Bronchoscopic findings at this time were necrosis of the posterior half of the bronchial stump and a small fistula at the posterior end of the stump. He died on postoperative day 31.

Discussion

Blood supply is essential to the healing of the bronchial stump. Among factors that can affect BMBF,[1-4] we investigated the effect of lymphadenectomy, chemotherapy, and chemoradiation therapy in this study.

With regard to lymphadenectomy, our results showed no significant reduction of BMBF and satisfactory healing of the bronchial stump in group A, indicating that BMBF was preserved adequately after lymphadenectomy. The bronchial microcirculation has two blood sources: the bronchial arteries and the pulmonary circulation.[8] Cutting of the bronchial artery seems to reduce bronchial microcirculation. However, this reduction may be compensated for by well-developed arteriolar communications in the bronchial wall and increased pulmonary blood flow to the bronchial tree,[7] thus preserving BMBF after lymphadenectomy. One of the patients whose bronchial stump showed ischemic changes had a 10-year history of insulin-dependent diabetes mellitus and had had a myocardial infarction 2 years before the operation. When his bronchial stump was closed, the tensile strength was strong. These factors may have affected healing of the bronchial stump.

As to the effect of chemotherapy on bronchial stump healing, it can lead to injury. Anticancer drugs have some injurious effects on vessel walls. One patient of group B had ischemic changes at the bronchial stump. He had no history of serious illness, and there were no technical problems during surgery. Because his flow values at the bronchial stump were moderately depressed throughout the course, chemotherapy may have affected the BMBF. As a whole, however, our data showed no significant reduction of BMBF throughout the course of these measurements, and healing of the bronchial stump in group B was good. These data suggest that chemotherapy generally does not have serious effects on BMBF and healing of the bronchial stump.

However, the preoperative values of BMBF in group C were significantly lower in comparison with those in groups A and B. Because BMBF at the sites outside of the radiation field was comparable with the control value, the cause of the decrease in BMBF seems chiefly to be the effect of radiation and not chemotherapy. The intraoperative BMBF was significantly decreased only in group C. Of 8 patients in group C, a bronchopleural fistula developed in 1 patient, and ischemic changes were observed in 3 with low intraoperative BMBF values. As mentioned earlier, bronchial microcirculation is generally preserved, even with surgery. However, radiation can damage the microcirculation by hyalinization of arterioles and fibrosis,[5,6] preventing compensation from arteriolar communications. This may have resulted in a decrease in BMBF intraoperatively and poor healing of the bronchial stump in group C. Because the postoperative value was comparable with the preoperative one, BMBF seems to recover within 8 to 10 days after surgery. These results suggest the importance of the existence of a compensatory mechanism in BMBF in the early postoperative period. According to our data, we cannot predict preoperatively which patient will have such compensatory capacity. Therefore this capacity is potentially decreased in all patients after chemoirradiation. Not all patients in group C had low preoperative and intraoperative flow despite high-dose irradiation. This is probably because sensitivity to radiation therapy varies among patients.

Our results of chemoradiation effects on BMBF cannot be directly applied to the cases with induction settings. This is because all patients in group C were in the subacute and late periods after radiation therapy; intervals between irradiation and surgery were from 2 months to 5 years. In the planned induction chemoradiation setting patients are operated on within 4 weeks after radiation therapy, corresponding to the acute period. Furthermore, in this study the radiation dose was 60 Gy, although it is commonly 40 to 45 Gy in the induction setting. In general, hyalinized changes in small vessels and fibrosis were observed in the subacute and late periods after radiation therapy. In the early (or acute) period, tissue shows reactive congestion, edema, and inhibition of capillary proliferation.[5] This explains why BMBF may decrease in the acute period as well. In fact, it has been reported that BMBF was reduced in the acute period in experiments in mongrel dogs.[6]

Clinically, bronchial complications seem to increase when the preoperative radiation dose exceeds 35 to 40 Gy.[9-11] This was supported by the experiments by Inui and colleagues.[6] They concluded that the safe dose of preoperative radiation was 36 Gy or less. According to their data, healing of the bronchial anastomosis was closely related to regional mucosal blood flow. When the dosage exceeded 36 Gy, the blood flow decreased to less than 60% of the preoperative level, and bronchial complications markedly increased. Therefore precautions are needed to avoid bronchial complications when irradiation exceeds doses of 35 to 40 Gy. Laser Doppler flow may become an excellent predictor of bronchial complications. At this time, however, the data are insufficient because the number of patients investigated in this study was small. Therefore we recommend that the bronchial stump be covered with pedicle flaps for prophylaxis against bronchopleural fistula[12,13] after chemoradiation therapy. Preservation of bronchial arteries may be useful, but this is very difficult because there is marked fibrosis around the hilum. We covered all the bronchial stumps in group C patients with an intercostal muscle pedicle flap.[14] Omentoplasty is an excellent method as well.

Laser Doppler flowmetry has been used as a reliable method for clinical investigation of microvascular perfusion in various organs.[15,16] There are also many reports on the use of this method in respiratory organs.[4,6,7,17] It is a noninvasive and repeatable method. Reproducibility was reported to be satisfactory,[7] which was further supported by our data.

Patients in group C were not homogeneous at least as to the intervals between radiation therapy and surgery and kinds of anticancer agents given. Moreover, the number of patients in groups B and C was small. Therefore we have reported limited evidence supporting the effects of preoperative therapy. Assuming that BMBF may reduce after the commonly used induction programs, adequate evaluation will be required in a prospective study in a number of patients treated in this fashion.

Conclusion

We investigated the effects of preoperative therapy on the bronchial perfusion at the time of surgery and the healing of the bronchial stump. The following results were suggested: (1) lymphadenectomy and chemotherapy had little effect on BMBF and the healing of the bronchial stump and (2) preoperative chemoradiation therapy decreased BMBF not only preoperatively but also intraoperatively and had adverse effects on healing of the bronchial stump.

REFERENCES

1. Faber LP, Kittle CF, Warren WH, Bonomi PD, Taylor SG IV, Reddy S, et al. Preoperative chemotherapy and irradiation for stage III non–small cell lung cancer. Ann Thorac Surg 1989;47: 669-77.
2. Fowler WC, Langer CJ, Curran WJ, Keller SM. Postoperative complications after combined neoadjuvant treatment of lung cancer. Ann Thorac Surg 1993;55:986-9.
3. Martini N, Rigas JR, Pisters KMW, McCormack PM, Rusch VW, Ginsberg RJ, et al. Preoperative chemotherapy for stage IIIa (N2) lung cancer: the Sloan-Kettering experience with 136 patients. Ann Thorac Surg 1993;55:1365-74.
4. Inui K, Wada H, Yokomise H, Lee M, Yamazaki F, Aoki M, et al. Evaluation of a bronchial anastomosis by laser Doppler velocimetry. J Thorac Cardiovasc Surg 1990;99:614-9.
5. Muehrcke DD, Grillo HC, Mathiesen DJ. Reconstructive airway operation after irradiation. Ann Thorac Surg 1995;59:14-8.
6. Inui K, Takahashi Y, Hasegawa S, Hirai T, Yokomise H, Hitomi S, et al. Effect of preoperative irradiation on wound healing after bronchial anastomosis in mongrel dogs. J Thorac Cardiovasc Surg 1993;106:1059-64.
7. Sundset A, Hansen G, Haanaes OC, Line PD, Kverneb K. Human bronchial perfusion evaluated with endoscopic laser Doppler flowmetry. Int J Microcirc: Clin Exp 1993;13:233-45.
8. Kröll F, Karlsson JA, Persson OG. Tracheobronchial microvessels perfused via the pulmonary artery in guinea-pig isolated lungs. Acta Physiol Scand 1987;129:445-46.
9. Mathisen DJ, Grillo HC, Vlahakes GJ, Daggett WH. The omentum in the management of complicated cardiothoracic problems. J Thorac Cardiovasc Surg 1988;95:677-84.
10. Warram J. Preoperative irradiation of cancer of the lung: final report of a therapeutic trial. Cancer 1975;36:914-25.
11. Tsubota N, Simpson WJ, Van Nostrand AWP, Pearson FG. The effect of preoperative irradiation on primary tracheal anastomosis. Ann Thorac Surg 1975;20:152-60.
12. McGovern EM, Trastec VF, Pairolero PC, Payne WS. Completion pneumonectomy: indications, complications and results. Ann Thorac Surg 1988;46:141-6.
13. Regnard JF, Icard P, Deneuville M, Jauffret B, Magdeleinat P, Levi JF, et al. Lung resection after high doses of mediastinal radiotherapy (sixty grays or more). J Thorac Cardiovasc Surg 1994;102:607-10.
14. Yamamoto R, Inoue K, Hori T, Takehara S, Kaji M, Kinoshita H. Intercostal muscle pedicle flap for prophylaxis against bronchopleural fistula after pulmonary resection. Osaka City Med J 1994;40:99-105.
15. Ahn H, Lindhagen J, Nilsson GE, Salerud EG, Jodal M, Lundgren O. Evaluation of laser Doppler flowmetry in the assessment of intestinal blood flow in cat. Gastroenterology 1985;88:951-7.
16. Kverneb K, Lunde OC, Stranden E, Larsen S. Human gastric blood circulation evaluated by endoscopic laser Doppler flowmetry. Scand J Gastroenterol 1986;21:685-92.
17. Yokomise H, Wada H, Inui K, Lee M, Aoki M, Hitomi S. Application of laser Doppler velocimetry to lung transplantation. Transplantation 1989;48:550-4.